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The association between toxoplasma and the psychosis continuum in a general population setting

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ABSTRACT

Toxoplasma gondii infection is associated with increased risk for psychosis. However, the possible association between *T. gondii* and psychotic-like symptoms in the general adult population is unknown.

We investigated whether *T. gondii* is associated with psychotic-like symptoms and psychosis diagnoses using data from Health 2000, a large cross-sectional health survey of the Finnish general population aged 30 and above. Seropositivity to toxoplasma was defined as a cutoff of 50 IU/ml of IgG antibodies. Lifetime psychotic-like symptoms were identified with section G of the Composite International Diagnostic Interview, Munich version (M-CIDI). Symptoms were considered clinically relevant if they caused distress or help-seeking or there were at least three of them. Lifetime psychotic disorders were screened from the sample and were diagnosed with DSM-IV using SCID-I interview and information from medical records. All data were available for 5906 participants. We adjusted for variables related to *T. gondii* seropositivity (age, gender, education, region of residence, cat ownership, and C-reactive protein measuring inflammation) in regression models.

We found that *T. gondii* seropositivity was significantly associated with clinically relevant psychotic-like symptoms (OR 1.77, $p = 0.001$) and with the number of psychotic-like symptoms (IRR = 1.55, $p = 0.001$). The association between toxoplasma and diagnosed psychotic disorders did not reach statistical significance (OR 1.45 for schizophrenia).

In a large sample representing the whole Finnish adult population, we found that serological evidence of toxoplasma infection predicted psychotic-like symptoms, independent of demographic factors and levels of C-reactive protein. Toxoplasma infection may be a risk factor for manifestation of psychotic-like symptoms.

1. Introduction

Toxoplasma gondii (*T. gondii*) infection is associated with increased risk of psychosis (Yolken and Torrey, 2008). In a recent meta-analysis, *T. gondii* seropositivity was associated with schizophrenia (odds ratio (OR) 1.8, 95% confidence interval (CI) 1.5–2.2) and with bipolar disorder (OR 1.5, 95% CI 1.1–2.2) (Sutterland et al., 2015). The OR was higher in patients with recent-onset than in chronic schizophrenia. High serointensity was associated with higher odds of schizophrenia, and the OR also varied by region, decreasing with higher seroprevalence in the population (Sutterland et al., 2015).

Increased risk of toxoplasma infection *before* the onset of schizophrenia was reported in the meta-analysis by Sutterland et al. (2015) with 1.3 OR (95% CI 1.1–1.6). However, fewer studies have investigated whether *T. gondii* is associated with subclinical psychotic-like symptoms, which may indicate subsequent psychosis risk (Schultze-Lutter et al., 2015). High serointensity associated with higher OR for schizophrenia, and the OR also varied by region and by the seroprevalence in the general population. In a Dutch adolescent population-based cohort study, toxoplasma was not associated with subclinical psychotic symptoms (Wang et al., 2011). In contrast, in young people at ultra-high risk (UHR) for psychosis, seropositivity to *T. gondii* related to more severe psychiatric symptoms and positive symptoms (Amminger et al., 2007).

In this study, we used data from a large Finnish general population survey to investigate whether *T. gondii* seropositivity and serointensity are associated with psychotic disorders and with subclinical

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psychotic-like symptoms. Thus, we looked at psychotic symptoms distributed along a continuum at varying levels of severity (van Os et al., 2009).

2. Methods

2.1. Participants

Data used in this study was from the Health 2000 (BRIF8901), a nationally representative survey of the Finnish population conducted in 2000–2001 (Aromaa and Koskinen, 2004). Adults aged 30 years and over were sampled using stratified two-staged cluster sampling ($N = 8028$). Individuals were chosen to the study to be representative of their age and gender group in the area where they lived. The protocol included a home interview and health examination at the local health care center or, for those unable to attend, a condensed interview and health examination at home or in an institution (Aromaa and Koskinen, 2004). Fig. 1 shows the participant flow diagram in the Health 2000 survey.

All participants gave written informed consent and the study was approved by the ethics committees of the Hospital District of Helsinki and Uusimaa and the National Institute for Health and Welfare.

2.2. Toxoplasma

Plasma samples were collected as a part of the participants' health examination. Immunoglobulin G (IgG) antibodies against *T. gondii*, indicating previous infection, were performed by solid phase enzyme immunoassay. Whole tachyzoite lysate from Ross South Labs, Spanish Fork Utah, USA was used, employing methods as previously described by Dickerson et al. (2007). Comparisons to standards with known levels of antibody were used to convert sample values to international units. We used 50 IU/ml as the cut-off for seropositivity, as in Sugden et al. (2016). In addition, serointensity, defined as the quantitative level of antibody in IU/ml, was analyzed as a continuous variable.

2.3. Psychotic-like symptoms

Lifetime psychotic-like symptoms were assessed using the Finnish translation of the Composite International Diagnostic Interview, Munich version (M-CIDI) (Wittchen et al., 1998), which was a part of the health examination (Pirkola et al., 2005).

Psychotic-like symptoms were assessed in section G of the interview. Participants were shown with a list of 23 psychotic-like experiences (Table 1) and asked if they had ever experienced any of them. Five of the experiences are hallucinatory (17–21) and 16 delusional (1–14), with two symptoms (22 and 22A) probing catatonic-like symptoms.

If any of the presented symptoms were endorsed, questions concerning the clinical relevance of the experiences were asked. Using a previously formed definition (Perälä et al., 2007), symptoms were considered clinically relevant if the person reported at least three symptoms, if the person had discussed the symptom(s) with a doctor or other professional, or if the symptom(s) had interfered with normal life.

In addition, the number of psychotic-like experiences reported by the person (0–23 symptoms) was used as a continuous variable in this study.

2.4. Psychotic disorders

Lifetime psychotic disorders were identified from the Psychoses in Finland study, which was a substudy of the Health 2000 survey (Perälä et al., 2007). Psychotic disorders were screened from the Health 2000 sample using the M-CIDI (clinically relevant symptoms as defined earlier), self-reported diagnoses, medical examination, and national register. The register screen included hospital treatment because of a diagnosis of any psychotic or bipolar disorder, free outpatient antipsychotic medication for severe psychotic and other severe mental disorders, and disability

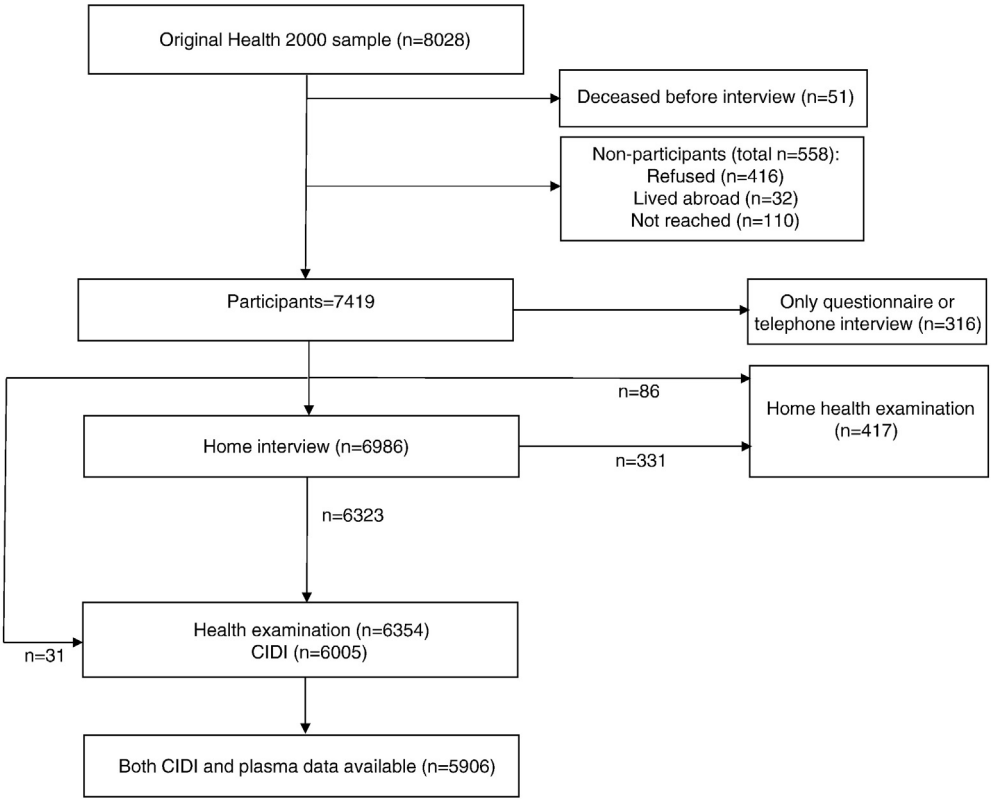

Fig. 1. Participant flow diagram in the Health 2000 study.

Table 1
The questions assessing psychotic-like symptoms with endorsement proportions.

Symptom	% [95% CI]
1. Have you ever believed people were spying on you?	0.81 [0.57, 1.05]
2. Was there ever a time when you believed people were following you?	2.21 [1.85, 2.57]
2B. Have you been convinced that people you saw talking to each other were talking about you or laughing at you?	6.52 [5.81, 7.23]
3. Have you ever believed that you were being secretly tested or experimented on?	0.30 [0.15, 0.44]
4. Have you ever believed that someone was plotting against you or trying to hurt you or poison you?	1.51 [1.21, 1.81]
5. Have you ever been convinced that someone you had not met was in love with you?	0.55 [0.35, 0.76]
6. Have you ever been unreasonably convinced that your spouse or partner was being unfaithful, although ^AS1^ told you that was not true?	2.48 [2.05, 2.91]
7. Have you ever believed that someone was reading your mind?	1.50 [1.15, 1.85]
8. Have you ever been convinced you could actually hear what another person was thinking, even though he or she was not speaking?	0.37 [0.20, 0.53]
9. Have you ever been convinced that others could hear your thoughts?	0.28 [0.16, 0.40]
10. Have you ever been convinced that you were under the control of some power or force, so that your actions and thoughts were not your own?	0.84 [0.62, 1.05]
11. Have you ever been convinced that strange thoughts, or thoughts that were not your own, were being put directly into your mind?	0.24 [0.12, 0.37]
12. Have you ever been convinced that someone or something could take or steal your thoughts out of your mind?	0.14 [0.04, 0.23]
13. Have you ever been convinced that you were being sent special messages through television or the radio, or that a program had been arranged just for you alone?	0.24 [0.11, 0.37]
13B. Have you felt that a book, or newspaper, or song was meant only for you and no one else?	0.42 [0.25, 0.59]
14. Have you ever felt strange forces working on you, as if you were being hypnotised or magic was being performed on you, or you were being hit by X-rays or laser beams?	0.66 [0.43, 0.88]
17. Have you ever seen something or someone that others who were present could not see — that is, had a vision or hallucination when you were completely awake?	0.88 [0.64, 1.12]
18. Have you more than once heard things other people couldn't hear, for example sounds or something like a voice?	0.83 [0.61, 1.05]
20. Have you ever been bothered by strange smells around you that nobody else seemed to be able to smell, perhaps even unusual odours coming from your own body?	0.42 [0.26, 0.59]
20C. Have you ever had strange tastes in your mouth that could not be explained by anything you had eaten or put in your mouth?	0.25 [0.12, 0.37]
21. Have you ever had unusual feelings on your skin or inside your body — like being touched when nothing was there or feeling something moving inside your body?	0.96 [0.72, 1.20]
22. Have you ever had a time when you were unable to move at all when it wasn't due to a physical or other medical reason?	0.27 [0.14, 0.40]
22A. Have you ever had a time when you moved constantly and couldn't stop when it wasn't due to a physical or other medical reason?	0.44 [0.27, 0.61]

CI, confidence intervals.

pension because of any psychotic disorder, bipolar disorder, or major depressive disorder. Those selected by the screens were then re-interviewed with the Structured Clinical Interview for DSM-IV (SCID-I, First et al., 1997). Best-estimate DSM-IV diagnoses were formed by combining information from the SCID interview with information from all medical records from lifetime mental health treatment contacts. A graphical presentation on the participants in the Psychoses in Finland study can be seen in the Supplementary Fig. 1.

Participants were grouped as follows (number of those with available plasma samples in parenthesis): 1) any psychotic disorder ($N = 155$), 2) functional psychosis (not substance induced or caused by a general medical condition, $N = 132$), 3) schizophrenia ($N = 41$), 4) non-affective psychosis other than schizophrenia (schizoaffective disorder, schizophreniform disorder, psychotic disorder not otherwise specified, brief psychotic disorder, or delusional disorder, $N = 56$), or 5) affective psychosis (bipolar I disorder or major depressive disorder with psychotic features, $N = 35$).

2.5. Other variables

We used age, sex, education, and region of residence as sociodemographic variables in the analyses. Education was classified as basic (only compulsory) education, secondary education (high school, vocational education), and high education (degree from higher vocational institutions, polytechnics or universities) (Aromaa and Koskinen, 2004). Current region of residence was categorized based on the university hospital districts as Northern, Eastern, Western, Southwestern, and Southern Finland.

Cat ownership was asked about in a questionnaire and categorized as current, previous, and never. This variable was used in the models because domestic cats are a potential source of toxoplasma infection and cats in Finland commonly are seropositive for toxoplasma (Jokelainen et al., 2012). In our previous work, we found an association between cat ownership and *T. gondii* (Suvisaari et al., 2017). Previous studies have found an association of childhood cat ownership with later schizophrenia (Torrey et al., 2015), but not to psychotic symptoms in adolescence (Solmi et al., 2017).

Serum high-sensitivity C-reactive protein (CRP) level was used to measure inflammation as described previously (Heikkilä et al., 2011). It was analyzed from serum samples taken at the same time as plasma samples from which toxoplasma antibodies were measured. Higher CRP levels were associated with *T. gondii* seropositivity in our previous study (Suvisaari et al., 2017).

2.6. Statistical analysis

Statistical analyses were conducted taking into account the two-stage cluster sampling design using Intercooled Stata 11.0 (StataCorp, 2009). In addition, poststratification weights were used to adjust for the oversampling of individuals aged 80 years and over and non-response.

The presence of clinically relevant psychotic-like symptoms, the number of psychotic-like symptoms and the prevalences of psychosis diagnoses in the toxoplasma seropositive and seronegative groups were calculated as predictive margins from logistic regression analysis or negative binomial model adjusting for age and sex (Graubard and Korn, 1999). Linear regression was used to calculate group differences in age and serointensity.

Next, to control for other variables associated with *T. gondii* seropositivity in our previous work using the same population and the 50 IU/ml cutoff (Suvisaari et al., 2017), we included gender, age, education, region of residence, CRP, and cat ownership as covariates besides *T. gondii*.

Analyses were repeated excluding those with a psychosis diagnosis to investigate the association between psychotic-like symptoms and *T. gondii* at the subclinical level.

Finally, the same regression analyses were conducted using serointensity as a continuous variable, after logarithmic transformation for normalization of the serointensity variable.

3. Results

3.1. Psychotic-like symptoms

5906 participants with toxoplasma infection data and CIDI interview data were included (Table 2). Of these participants, 11.6% said that they had experienced some of the presented psychotic-like symptoms. 6.7% reported one symptom, 2.6% two symptoms, and 2.4% three or more symptoms. The endorsement proportions for the individual 22 symptoms, ranging from 0.1 to 6.5%, are presented in Table 1. There was no gender difference for the total number of symptoms or delusional symptoms but women reported more hallucinatory symptoms than men ($p = 0.018$). Younger age was associated with having more symptoms ($p < 0.001$), specifically delusional symptoms ($p < 0.001$).

1.8% of the participants had talked about the symptoms with a doctor or another mental health professional and 0.8% reported that the symptom had interfered with normal life. Altogether, symptoms were clinically relevant in 4.0% of the cases, with no significant gender difference. Younger age was associated with presence of clinically relevant psychotic-like symptoms ($p = 0.046$).

3.2. Psychosis diagnoses

Any lifetime psychotic disorder was diagnosed in 2.6% and schizophrenia in 0.7% of the participants, Table 2. Diagnoses were not related to age or gender except for affective psychosis, which was diagnosed in 0.8% of men and 0.4% of women ($p = 0.041$).

3.3. Toxoplasma and psychotic-like symptoms

Seroprevalence of *T. gondii* in this sample was 19.4% (95% CI 18.1–20.8). Clinically relevant psychotic-like symptoms were more common among toxoplasma seropositive than among seronegative participants ($p = 0.001$, Fig. 2). In a logistic regression model, toxoplasma seropositivity was significantly associated with clinically relevant psychotic-like symptoms when age, gender, education, region of residence, cat ownership, and CRP were controlled for (Table 3).

Participants seropositive for *T. gondii* reported more psychotic-like symptoms than the seronegative participants ($p = 0.027$, Fig. 3). Predicting the number of reported psychotic-like symptoms in a negative binomial regression model, toxoplasma seropositivity was a significant predictor (Table 4).

Looking at the number of hallucinatory symptoms separately, toxoplasma seropositivity (incidence rate ratio (IRR) = 1.80, 95% CI 1.14–2.83, $p = 0.011$) was a significant predictor (especially concerning auditory hallucinations, see Supplementary Tables). The number of delusional symptoms was also associated with toxoplasma (IRR = 1.48, 95% CI 1.13–1.93, $p = 0.004$).

The regression analyses were repeated after excluding those with a lifetime DSM-IV psychotic disorder. Toxoplasma seropositivity predicted both clinically relevant psychotic-like symptoms (OR 1.86, 95% CI 1.24–2.79, $p = 0.003$) and the number of psychotic-like symptoms (IRR = 1.44, 95% CI 1.10–1.89, $p = 0.008$) in participants never diagnosed with psychotic disorder.

3.4. Toxoplasma and psychosis diagnoses

Those with and without psychotic disorders assessed did not differ in seroprevalence for toxoplasma (Table 2).

In logistic regression, any psychotic disorder was not predicted by toxoplasma seroprevalence but there was a trend towards an association (OR 1.45, 95% CI 0.99–2.14, $p = 0.057$).

In separate models, toxoplasma was neither significantly associated with schizophrenia (OR 1.45, 95% CI 0.70–3.03, $p = 0.320$) nor the other psychosis diagnoses.

3.5. Results using the serointensity

When antibodies to toxoplasma gondii were investigated as a continuous variable instead of dichotomous seropositivity, the findings were similar. In a logistic regression model of clinically relevant psychotic-like symptoms, higher levels of antibodies against toxoplasma (OR 1.35, 95% CI 1.15–1.59, $p < 0.001$) remained as the only significant predictor, when age, gender, education, region of residence, cat ownership, and CRP were controlled for. The number of reported psychotic-like symptoms was predicted by toxoplasma serointensity (IRR = 1.21, 95% CI 1.07–1.36, $p = 0.002$). These results were repeated with the subset of participants who had never been diagnosed with psychotic illness.

Psychoses were not associated with toxoplasma serointensity (OR for any psychosis 1.18, 95% CI 0.98–1.43; OR for schizophrenia 1.12, 95% CI 0.79–1.59), when age, gender, education, region of residence, cat ownership, and CRP where controlled for.

Table 2
Characteristics, psychotic-like symptoms and psychosis diagnoses of the participants, calculated by linear regression, negative binomial regression, or logistic regression adjusting for age and sex.

	Total, $N = 5906$[a]	Seropositive, 19.4%[b]	Seronegative, 80.6%[b]	Group difference
Females (%)	51.9 [50.6, 53.2]	59.8 [56.6, 63.0]	50.0 [48.6, 51.5]	**$p < 0.001$**
Age (years)	51.7 [51.3, 52.1]	54.9 [54.1, 55.7]	51.0 [50.5, 51.4]	**$p < 0.001$**
Toxoplasma serointensity (IU/ml)	27.0 [25.9, 28.1]	78.2 [76.0, 80.4]	14.7 [14.4, 15.0]	**$p < 0.001$**
Lifetime psychosis diagnoses (%)				
Any psychotic disorder	2.6 [2.2, 3.1]	3.4 [2.3, 4.4]	2.5 [2.0, 2.9]	$p = 0.069$
Functional psychosis	2.3 [1.9, 2.7]	2.7 [1.8, 3.7]	2.1 [1.7, 2.5]	$p = 0.167$
Schizophrenia	0.7 [0.5, 0.9]	0.9 [0.3, 1.4]	0.7 [0.4, 0.9]	$p = 0.459$
Other non-affective psychosis	0.9 [0.7, 1.2]	1.2 [0.6, 1.8]	0.9 [0.6, 1.2]	$p = 0.388$
Affective psychosis	0.6 [0.4, 0.8]	0.7 [0.2, 1.2]	0.6 [0.4, 0.8]	$p = 0.648$
Lifetime psychotic-like symptoms in CIDI-G				
Clinically relevant psychotic-like symptoms (%)	4.0 [3.4, 4.5]	5.9 [4.4, 7.3]	3.6 [3.0, 4.2]	**$p = 0.001$**
Number of all psychotic-like symptoms	0.23 [0.21, 0.26]	0.29 [0.23, 0.35]	0.22 [0.19, 0.24]	**$p = 0.027$**
Number of hallucinatory symptoms	0.03 [0.03, 0.04]	0.05 [0.03, 0.06]	0.03 [0.02, 0.04]	$p = 0.052$
Number of delusional symptoms	0.19 [0.17, 0.21]	0.23 [0.18, 0.28]	0.18 [0.16, 0.20]	$p = 0.052$

CIDI-G, G section of the Composite International Diagnostic Interview, Munich version.
Statistically significant results shown in bold.
[a] In the total group, proportions (%) or means [95% confidence intervals]. Adjusted for sampling design.
[b] In the subgroups, proportions (%) and means calculated as predictive margins [95% confidence intervals]. Adjusted for sampling design, age, and sex.

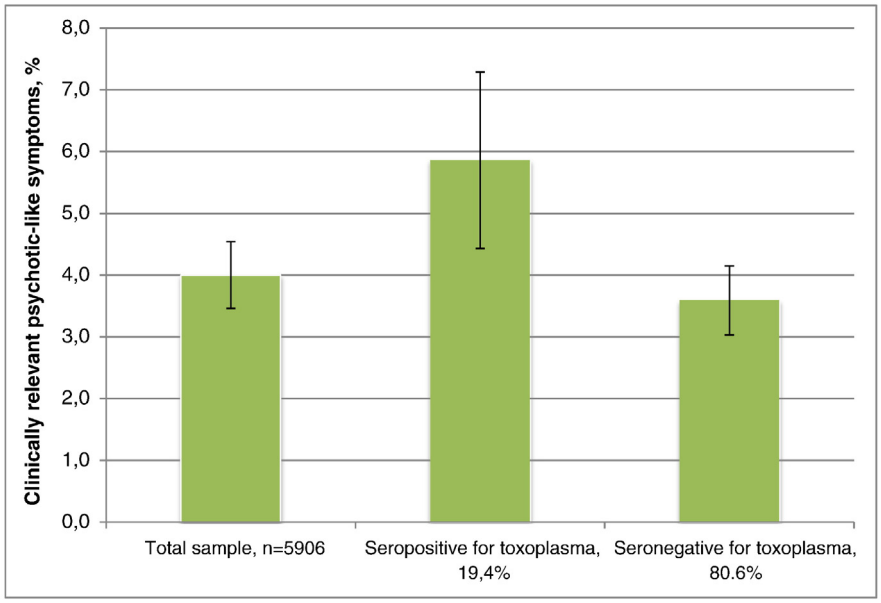

Fig. 2. The proportion of participants with clinically relevant psychotic-like symptoms with 95% confidence intervals.

4. Discussion

4.1. The association between toxoplasma and the psychosis continuum

We used a large general population study sample to investigate whether serological evidence of toxoplasma infection is associated with the psychosis continuum. While the association between infection and fully developed psychotic illnesses was not statistically significant, the infection did increase the vulnerability for psychotic-like symptoms in the study population representative of the whole adult population in Finland.

T. gondii seropositivity and serointensity were associated with both the number of psychotic-like symptoms and with clinically relevant psychotic-like symptoms. Adjusting for CRP levels, indicating inflammation, did not change the effect.

To our knowledge, the association between *T. gondii* and the subclinical positive dimension of psychosis in the general adult population has not been studied previously. In an adolescent population sample attenuated psychotic symptoms and toxoplasma were not correlated (Wang et al., 2011). However Wang and colleagues measured psychotic symptoms with the mean score of positive items in the Community Assessment of Psychic Experiences (CAPE), including also mild psychotic-like experiences. Compared to CAPE, the items of CIDI-G are tapping slightly more severe experiences.

Another previous study investigated antibodies against infectious agents associating with positive symptoms in an ultra-high risk (UHR) sample, suggesting that in some UHR individuals, onset of psychotic symptoms may be associated with toxoplasma infection (Amminger et al., 2007). Our positive finding of the association between positive symptoms and toxoplasma is consistent with their results, although the current sample was not selected for psychosis risk.

The most common experiences reported were referential thinking and suspicion (items 2, 2B, and 6). Similarly to a cross-national WHO surveys assessing 6 psychotic experiences with CIDI (McGrath et al., 2015), symptoms were more common among women compared to men. In the WHO study, the lifetime prevalence of psychotic experiences was lower (5.8%), however (McGrath et al., 2015).

Some people reporting psychotic-like experiences in our study have psychotic illnesses and for some, the symptoms express vulnerability for psychotic disorders. However, the association between *T. gondii* seropositivity and psychotic-like symptoms remained statistically significant after people with a lifetime diagnosis of psychotic disorder were excluded. According to previous work, also subclinical symptoms are associated with heightened risk for psychosis (Bak et al., 2003). Although they are mostly transitory, poorer outcome may emerge if additional risk factors arise (van Os et al., 2009). Moreover, psychotic symptoms are associated with worse health and functional capacity even when the symptoms do not reach the clinical threshold for psychosis (Nuevo et al., 2012). More longitudinal research is needed to address the question of whether toxoplasma has a role in the development of actual psychosis in those with attenuated psychotic symptoms.

It has been argued that elevated antibodies against toxoplasma could also be a *consequence* of psychopathology. That is why studying the antibodies before illness onset is beneficial. There are prospective studies such as Pedersen et al. (2011) using a large cohort, where individuals with high levels of IgG antibodies against toxoplasma had an elevated risk of developing schizophrenia during follow-up up to 16 years. The possible biological mechanisms between toxoplasma infection and symptoms in the psychosis continuum include altered dopamine transmission, neuro-inflammation, altered hormone

Table 3
Logistic regression model of clinically relevant psychotic-like symptoms; all variables entered in the model simultaneously. Reference category in parentheses.

	OR	95% CI for OR		Sig.
		Lower	Upper	
Gender (male)				
Female	1.20	0.89	1.64	0.233
Age	0.99	0.98	1.00	0.166
Education (basic)				
Secondary education	0.71	0.46	1.10	0.126
High education	0.92	0.60	1.41	0.703
Region of residence (Southern Finland)				
Southwestern Finland	0.61	0.31	1.18	0.142
Western Finland	0.76	0.52	1.12	0.165
Eastern Finland	0.98	0.65	1.47	0.917
Northern Finland	1.02	0.64	1.63	0.946
C-reactive protein (CRP)	1.00	0.98	1.02	0.866
Cat ownership (never)				
Previous	1.06	0.73	1.53	0.761
Current	0.92	0.55	1.55	0.757
Toxoplasma seroprevalence (negative)				
Positive	**1.77**	**1.26**	**2.48**	**0.001**

OR, odds ratio.
CI, confidence interval.
Statistically significant results shown in bold.

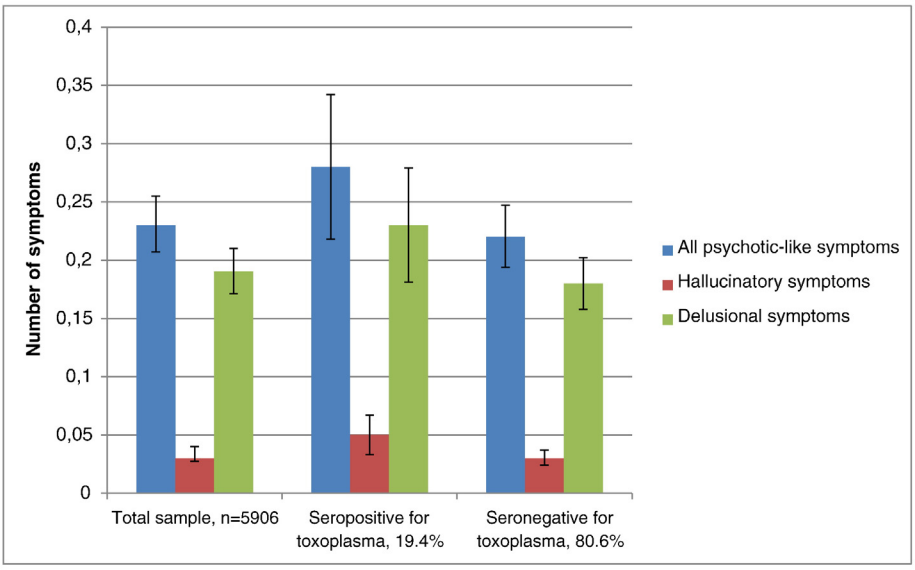

Fig. 3. Number of reported psychotic-like symptoms in the CIDI-G with 95% confidence intervals.

transmission, and effects to hippocampus and amygdala (Elsheikha et al., 2016;Severance et al., 2016). There are also epidemiological similarities between schizophrenia and toxoplasma (Yolken et al., 2009).

Only 5.9% of *T. gondii* seropositives had clinically relevant psychotic-like symptoms in the current sample. Hence, most people with a history of *T. gondii* infection do not develop psychotic-like symptoms. It may be the timing of primary infection that matters in respect of the impact, along with individual genetic factors, *T. gondii* strain (Xiao and Yolken, 2015), and type of initial infection.

In the current sample, the 1.45 OR for schizophrenia was similar to the 1.53 OR found in the European region in the meta-analysis by Sutterland et al. (2015). However, toxoplasma did not reach statistical significance predicting meeting criteria for DSM-IV psychotic disorders, although there was a trend towards an association ($p = 0.057$). One reason for this may be that psychotic diagnoses in the current study were lifetime and many individuals with psychosis had been ill for a long time. The sample size for diagnosed psychosis was also relatively small. Psychotic disorders were more common in toxoplasma seropositive participants, although the difference was not statistically significant.

Table 4
Negative binomial regression model of number of psychotic-like symptoms; all variables entered in the model simultaneously. Reference category in parentheses.

	IRR	95% CI for IRR		Sig.
		Lower	Upper	
Gender (male)				
Female	1.18	0.95	1.46	0.136
Age	**0.99**	**0.98**	**0.99**	**0.002**
Education (basic)				
Secondary education	**0.69**	**0.53**	**0.91**	**0.008**
High education	0.91	0.66	1.26	0.569
Region of residence (Southern Finland)				
Southwestern Finland	**0.56**	**0.39**	**0.82**	**0.003**
Western Finland	**0.56**	**0.39**	**0.81**	**0.002**
Eastern Finland	0.99	0.73	1.35	0.947
Northern Finland	1.04	0.75	1.45	0.815
C-reactive protein (CRP)	1.00	0.98	1.02	0.865
Cat ownership (never)				
Previous	0.97	0.73	1.30	0.840
Current	0.92	0.66	1.28	0.621
Toxoplasma seroprevalence (negative)				
Positive	**1.55**	**1.18**	**2.02**	**0.001**

IRR, incidence rate ratio.
CI, confidence interval.
Statistically significant results shown in bold.

4.2. Strengths and weaknesses

The strength of the current study is the large number of participants. The whole Finnish population aged 30 and above was represented in the Health 2000 study. However, Finland is a country with a relatively low *T. gondii* seroprevalence (von Hertzen et al., 2006), and in the European region, the association of toxoplasma with schizophrenia is lower than in many other regions of the world (Sutterland et al., 2015). The study was cross-sectional and timing of the infection could not be determined in the current study. IgM antibodies indicating acute infection were not investigated. The study also lacked information on socioeconomic background of the participants other than education.

Both psychotic illnesses and psychotic-like symptoms were investigated in this study. While microbial agents have been investigated in patients with established psychosis, not many studies have looked into the possible association between subclinical positive symptoms and infectious agents. However, the G section of the CIDI alone is not a sensitive method for screening psychotic disorders (Perälä et al., 2007;Kendler et al., 1996). Nevertheless, the number of psychotic-like symptoms endorsed in the CIDI interview has been found to correlate with a range of symptoms, including mood, sleep, energy, cognition, and functioning (Nuevo et al., 2012), indicating clinical relevance.

4.3. Conclusions

We found that people with serological reactions to *T. gondii* had elevated risk presenting with psychotic-like symptoms, pointing out need for efficient prevention of *T. gondii* infections. Further studies are needed to address the possible etiological effect of toxoplasma infection on the risk of transition to psychosis. If toxoplasma infection continues to appear as a risk factor for psychotic-like symptoms and emerging psychosis, this may affect the treatment of symptomatology across the psychosis continuum.

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Contributors

JS and RHY contributed to designing the study. ML and MT-H undertook the statistical analysis. TH was in charge of the statistical methods. ML managed the literature searches and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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Conflict of interest

Author ML has received financial compensation for an interview from Oy H. Lundbeck Ab/Otsuka Pharma Scandinavia AB in 2016. All other authors declare that they have no conflicts of interest.

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